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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/245,603	02/05/1999	DAVID T. CURIEL	678503-2012.2	5072

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EXAMINER	
MAKAR, KIMBERLY A	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 07/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/245,603	CURIEL ET AL.	
	Examiner	Art Unit	
	Kimberly A. Makar	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 November 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 12/1/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 05/01/2006 has been entered.

2. The examiner of your application has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Kimberly Makar, Ph.D. Art Unit 1636.

3. Claims 1-4, 9,11,16, 22-23, 31 and 32 have been canceled by applicant. New claims 33-54 have been added by applicant 05/01/2006 are pending. All prior rejections have been withdrawn.

Claim Objections

4. Claim 45 is objected to because of the following informalities: Claim 45 misspells the word transduce with "transducer". Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 33-54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 42 recites the limitation "claim 1". There is insufficient antecedent basis for this limitation in the claim. Claim 1 was canceled by applicant.

7. Claim 43 recites the limitation "claim 1". There is insufficient antecedent basis for this limitation in the claim. Claim 1 was canceled by applicant.

8. Claim 33 uses the phrase " a recombinant adenovirus adding a new binding specificity to an adenovirus" which is unclear and not defined in the specification. Does this refer to making a recombinant adenovirus with a new binding specificity? Does this refer to a recombinant adenovirus influencing the specificity of a wild-type adenovirus?

9. Claim 33 also uses the phrase "novel tropism." Tropism is not defined in the specification, thus the term "novel tropism" is unclear. What does this term encompass? Does the wild-type adenovirus have the "novel tropism" or is that a result of the altered binding specificity? How would a wild-type adenovirus retain "novel tropism"?

10. Additionally, claim 33 encompasses two adenoviruses, a "recombinant adenovirus" and "an adenovirus" yet uses the phrase "said adenovirus" to refer back to one. It is unclear as to which adenovirus "said adenovirus" is referring to. Thus a skilled artisan would be unable to determine the metes and bounds of the invention.

11. Claim 34 states the phrase "said adenovirus" when referring to claim 33. It is unclear as to which adenovirus "said adenovirus" refers.

12. Claim 35 states the phrase "said adenovirus" when referring to claim 33. It is unclear as to which adenovirus "said adenovirus" refers.

13. Claim 40 states the phrase "said adenovirus" when referring to claim 33. It is unclear as to which adenovirus "said adenovirus" refers.

14. Claim 45 states the phrase "said adenovirus" when referring to claim 33. It is unclear as to which adenovirus "said adenovirus" refers.

15. Claim 51 states the phrase "said adenovirus" when referring to claim 45. It is unclear as to which adenovirus "said adenovirus" refers.

16. Claim 45 is vague in that the claim depends on claim 33. Claim 45 writes, "introducing a ligand in to said HI loop domain according to claim 33." Claim 33 is a composition claim, not a method claim, to which applicant seems to refer to Claim 33 as. It is unclear if claim 45 intends to have all the limitations of the recombinant adenovirus recited in claim 33. Thus a skilled artisan would be unable to determine the metes and bounds of the invention.

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States

only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

18. Claims 33-44 are rejected under 35 U.S.C. 102(e) as being anticipated by Wickham et al (US Patent No. 5,846,782). Claims 33-44 teach a recombinant adenovirus comprising new binding specificity while retaining novel tropism, wherein the adenovirus comprises a fiber gene modified in the HI loop domain of the fiber knob by introduction of a ligand into said HI loop domain (claim 33). The adenoviral vector is further limited to achieve CAR-independent transfer (claim 34) and wherein the adenovirus further comprises an additional modification to said fiber knob ablating the native tropism of the adenovirus (claim 35). The adenoviral vector is further limited wherein the modified fiber knob retains it's ability to trimerize and its native biosynthesis profile (claim 36). The ligand for the adenoviral vector is selected from the group consisting of physiological ligands, anti-receptor antibodies, and cell-specific peptides (claim 37) or and RGD tripeptide sequence (claim 38) or the peptide sequence CDCRGDCFC (claim 39). The vector is further limited to encode a therapeutic gene (claim 40) and the gene is further limited to the herpes simples virus-thymidine kinase gene (claim 41). The vector is also limited wherein the native binding of the adenovirus is maintained (claim 42). The ligand insert into the adenovirus is inserted into a homogeneous serotype fiber (claim 43) and wherein the adenovirus is the serotype Ad5 and the fiber knob is also an Ad5 fiber knob (claim 44).

19. Wickham et al. teach a recombinant adenovirus that results in, "an ability to direct entry into cells...that is more efficient than entry into cells of a vector that is identical except for comprising a wild-type adenoviral protein, and/or an ability to direct entry into

cells that adenovirus comprising the wild-type fiber protein does not infect/transduce." Column 3, lines 50-58. Specifically, Wickham teaches that the adenovirus is modified in the fiber gene by the addition of a ligand into the fiber gene which can comprise, "an antibody, or a ligand for a cell surface binding site" (column 5, lines 51-52). Wickham specifically teaches the use of native Ad5 adenovirus for the backbone (column 13, line 10), as well as Ad5 fiber proteins (column 5, lines 30-31) and Ad5 HI loop regions (column 8 lines 8-10). Wickham also teaches that the non-critical loop regions "provide convenient sites at which peptide motifs can be inserted" (column 7, lines 34-35). Specifically Wickham defines the non-critical loop regions of the Ad5 fiber knob as the AB loop, the CD loop, the DG loop, the GH loop, the IJ loop, and the HI loop (column 7 lines 60- column 8 lines 2). Wickham states, "The nonnative amino acid sequence is inserted into or in place of a protein sequence in a loop of the knob of the chimeric adenoviral protein. Optionally, the fiber protein loop is selected from the group consisting of the AB, CD, DG, GH, and IJ loops, and desirably is the HI loop" (column 8, lines 48-55).

20. Wickham teaches that the recombinant adenoviral vector ligands can be used for cell targeting that adds new binding specificity. Wickham states, "a cell surface binding site according to the invention preferably one that previously was inaccessible to interaction with a wild-type adenoviral fiber protein, or was accessible only at a very low level...the insertion of the nonnative amino acid sequence in the chimeric fiber protein thus desirably imparts upon the chimeric fiber protein an ability to bind to a binding site present on a cell surface which wild-type fiber proteins does not bind, or binds with very

low affinity" (column 6, lines 28-39). Since the chimeric adenovirus is capable of retaining its ability to continue to bind its native receptor, the native binding of the adenovirus is maintained. However, Wickham also teaches that the addition of a ligand into the HI loop of the Ad5 adenovirus results in CAR-independent transfer where the addition of the ligand "allows direct entry into the cells...with a cellular receptor other than the fiber receptor" (column 6, lines 39-44). The identification of the CAR-receptor's role as the AD5 fiber receptor was identified in 1997 (Bergelson, et al. Science, 1997) two years after the filing date of Wickham et al. The placement of the ligand in place of (rather than simply inserted between) (column 8 lines 50-53) a protein sequence in the loop which renders the virus incapable of CAR-dependent transfer. Additionally, Wickham teaches that the chimera adenovirus can be mutated such that the fiber receptor binding domain is mutated such that it no longer binds its receptor and specific receptor binding domains are incorporated into the fiber protein instead (column 17, lines 52-63). Thus this mutation would ablate the native tropism of the modified adenovirus while allowing the modified adenovirus to infect alternate cells.

21. Wickham teaches that the adenoviral vector retains its ability to trimerize (column 16, lines 18-31) and that the vector can be a wild-type vector (ie retains its native biosynthesis profile) (column 13, lines 23-24). Furthermore, Wickham teaches that the ligand can comprise an RGD tripeptide sequence (column 17, lines 25-35) and specifically the CDCRGDCFC sequence (Column 30, lines 26-28). Wickham also teaches that the chimeric adenovirus further comprises a therapeutic gene (column 13, lines 57-61), and specifically teaches the inclusion of the Herpes simplex virus

thymidine kinase gene as that therapeutic gene (column 14, lines 37-59). Thus Wickham et al teaches the claimed invention.

22. Claims 45-54 are rejected under 35 U.S.C. 102(e) as being anticipated by Wickham et al (US Patent No. 5,846,782). Claims 45-54 state a method of increasing the ability of an adenovirus to traduce a cell wherein the cell has native adenoviral receptors, comprising the steps of: modifying the fiber gene in the HI loop domain of the fiber knob of said adenovirus by introducing a ligand into said HI loop domain (claim 45). The method is further limited to comprise a vector is inserted with ligands consisting of physiological ligands, anti-receptor antibodies and cell-specific peptides (claim 46) or and RGD tripeptide (claim 47) or a peptide having the sequence CDCRGDCFC (claim 48). The method is further limited to a tumor cell (claim 49) wherein the tumor cell is in vitro, in vivo and ex vivo (claim 50). The method further limits the adenovirus vector comprises a therapeutic gene (claim 51) and that the native binding of the adenovirus is maintained (claim 52). Furthermore, the method is limited wherein the ligand inserted into a homogenous serotype fiber (claim 53) and that the adenovirus and the fiber knob is an Ad5 fiber knob (claim 54).

23. Wickham et al. teach a method for enhanced transfer of a recombinant adenovirus into a cell that results in, "an ability to direct entry into cells...that is more efficient than entry into cells of a vector that is identical except for comprising a wild-type adenoviral protein, and/or an ability to direct entry into cells that adenovirus comprising the wild-type fiber protein does not infect/transduce." Column 3, lines 50-58. Specifically, Wickham teaches that the adenovirus is modified in the fiber gene by the

addition of a ligand into the fiber gene which can comprise, "an antibody, or a ligand for a cell surface binding site" (column 5, lines 51-52). Furthermore, Wickham teaches that the ligand can comprise an RGD tripeptide sequence (column 17, lines 25-35) and specifically the CDCRGDCFC sequence (Column 30, lines 26-28).

24. Additionally, Wickham teaches that the method is useful for the treatment of cancer (column 17, lines 3-17) thus can target those cells, specifically targeting tumor cells (column 19, line18). Wickham teaches that the method can be used in vivo, in vitro or ex vivo (column 18, lines 23-24 and line 60 through column 19, line 18). Wickham also teaches that the method utilizes chimeric adenovirus further comprising a therapeutic gene (column 13, lines 57-61) and a method which utilizes an adenovirus still capable of native receptor binding (column 6, lines 28-39). Wickham specifically teaches the use of native Ad5 adenovirus for the backbone (column 13, line 10), as well as Ad5 fiber proteins (column 5, lines 30-31) and Ad5 Hi loop regions (column 8, lines 8-10) in the method of enhancing the adenovirus ability to transduce cells. Thus Wickham et al teaches the claimed invention.

Conclusion

25. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Makar, Ph.D. whose telephone number is 571-272-4139. The examiner can normally be reached on 8AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

KAM/07/06/06

DAVID GUZO
PRIMARY EXAMINER